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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/771,440	02/05/2004	Michal Danicly	26003	3178
67801	7590	07/06/2011		
MARTIN D. MOYNIHAN d/b/a PRTSI, INC. P.O. BOX 16446 ARLINGTON, VA 22215			EXAMINER DUFFY, BRADLEY	
			ART UNIT 1643	PAPER NUMBER
			MAIL DATE 07/06/2011	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/771,440	DANIELY ET AL.
	Examiner	Art Unit
	BRAD DUFFY	1643

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 October 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 72.73.82.84.87.89.91 and 93 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 72.73.82.84.87.89.91 and 93 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>11/23/10</u> | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
5) <input type="checkbox"/> Notice of Informal Patent Application
6) <input type="checkbox"/> Other: _____ |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 27, 2010, has been entered.
2. The amendment filed October 27, 2010, is acknowledged and has been entered. Claims 72, 73 and 87 have been amended. Claims 83, 85, 86, 88, 90 and 92 have been canceled. Claim 93 has been newly added.
3. Claims 72, 73, 82, 84, 87, 89, 91 and 93 are pending in the application and are under examination.

Information Disclosure Statement

4. The references cited in the information disclosure statement filed November 23, 2010, are duplicate citations of citations provided on either the IDS filed April 9, 2008, or April 17, 2009. Accordingly, these references have been previously considered and the IDS filed November 23, 2010 has been crossed-out.

Grounds of Objection and Rejection Withdrawn

5. Applicant's amendments filed October 27, 2010, have obviated or rendered moot the grounds of rejection set forth in the previous Office action mailed April 29, 2010.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 72, 73, 82, 87, 89, 91 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bubendorf et al (Am J Clin Pathol., 116:79-86, 2001, of record) in view of Brown (Urol. Clin. NA., 27(1):25-37, 2000, of record).

As amended, the claims herein recite methods comprising:

(a) staining nucleated cells of a voided urine sample using a stain selected from the group consisting of May-Grunwald-Giemsa, Giemsa, Papanicolau and Hematoxylin-Eosin to thereby obtain stained nucleated cells;

(b) imaging said stained nucleated cells resultant of steps (a) so as to obtain images of said stained nucleated cells, and;

(c) analyzing a nucleus to cytoplasm ratio in transitional epithelial cells by said stain in said images of step (b) and identifying a single cell having a morphological abnormality which comprises a high nucleus to cytoplasm (N/C) ratio as compared to a transitional epithelial cell with a normal morphology, said morphological abnormality indicates that said single cell is suspicious as being a transitional cell carcinoma (TCC) cell, and subsequently;

(d) staining said stained nucleated cells resultant of step (a) using fluorescent in situ hybridization (FISH) to thereby obtain stained nucleated cells stained with FISH, and; subsequently;

(e) imaging said nucleated cells stained with FISH resultant of step (d) so as to obtain images of said nucleated cells stained with FISH; and subsequently;

(f) identifying in said images of step (e) a chromosomal abnormality associated with said transitional cell carcinoma in the same said single cell identified in step (c) having said morphological abnormality associated with transitional cell carcinoma; (see claim 72)

or methods comprising:

(a) obtaining a voided urine sample from the subject;

(b) identifying transitional cell carcinoma cells according to the method of claim 72; (see claim 73). Claim 88 further recites analyzing said transitional epithelial cells for a morphological abnormality selected from an enlarged nucleus, a considerable dark appearance of a cell or an irregular nuclear border as compared to a transitional epithelial cell with a normal morphology. Claims 89 and 91 are further drawn herein to said chromosomal abnormality being a polyploidy of chromosome 3, chromosome 7, chromosome 17 or loss of 9p21 locus. Claim 93 further recites that said nucleated cells

of the voided urine sample are cyto-centrifuged at a cell density of 300-500 cells per mm^2 prior to step (a).

Bubendorf et al teach methods of identifying transitional cell carcinoma cells or diagnosing bladder cancer from a voided urine sample comprising:

obtaining a voided urine sample from a subject

staining nucleated cells of the sample with Papanicolau to obtain stained nucleated cells;

imaging the stained nucleated cells, and;

identifying in the images cells having a morphological abnormality (see page 80, Materials and Methods) and methods of identifying transitional cell carcinoma cells or diagnosing bladder cancer from a voided urine sample comprising:

obtaining a voided urine sample from a subject

staining nucleated cells of the sample with DAPI and FISH probes from chromosomes 3, 7, 17 and 9p21 to obtain stained nucleated cells;

imaging said nucleated cells stained with FISH resultant so as to obtain images of said nucleated cells stained with FISH; and subsequently;

identifying in said images single target cells with morphological abnormalities like large nuclear size, irregular nuclear shape and patchy and then enumerating FISH signals on these same single cells staining to identify transitional cell carcinoma cells or diagnose bladder cancer.

(see entire document, e.g., page 80, Materials and Methods, page 81, left column and Tables 2 and 3).

Bubendorf et al does not expressly teach that transitional cell carcinoma cells can be identified by a high nucleus to cytoplasm (N/C) ratio.

This deficiency is made up for in the teachings of Brown. Brown teaches that other morphological abnormalities that identify transitional cells as suspicious as transitional carcinoma cells include cells with a high nucleus to cytoplasm (N/C) ratio and cells that are enlarged and identifying such abnormalities with a Papanicolau stain. (see entire document, e.g., page 27).

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to predictably substitute Papanicolaou stain for the DAPI stain of Bubendorf et al to identify a high nucleus to cytoplasm (N/C) ratio and other transitional cell carcinoma cell morphological abnormalities such as an enlarged nucleus, a considerable dark appearance of a cell or an irregular nuclear border as compared to a transitional epithelial cell with a normal morphology as taught by Brown and Bubendorf, to identify single target cells for further analysis using the FISH stains of Bubendorf et al to identify the same single cells as transitional cell carcinoma cells and diagnose bladder cancer in view of these references as a whole.

In this case, one of skill in the art would have appreciated that there are multiple art-recognized morphological abnormalities and multiple art-recognized stains that can identify the known morphological abnormalities of transitional cell carcinoma cells in voided urine samples and would have considered such art-recognized staining techniques and visualizing known morphological abnormalities as obvious variants of each other which can be predictably substituted one for the other in methods of identifying transitional cell carcinoma cells or monitored together to identify the same single cells as transitional cell carcinoma cells. Furthermore, because these stains and morphological abnormalities were all known in the art to identify transitional cells as transitional cell carcinoma cells and because methods of imaging the same single cells were known in the art, one of skill in the art clearly would have a reasonable expectation of success in identifying transitional cell carcinoma cells from a voided urine sample, by such methods, in view of the references.

Finally, with respect to claim 93, Bubendorf et al teach that the samples should be cytospun onto slides at a cell density between 100 to 400 per field and optimizing the density to 100 to 200 cells per visual field if more than 4000 cells were in a field (see page 80, left column). Accordingly, it is submitted that the prior art recognized that the cell density of cells on the cytospin slide was to be optimized and could be optimized by routine experimentation, such that a step of cytospinning the cells in a sample to a density of 300-500 cells per square mm would not have been considered inventive by one of skill in the art. Furthermore, the Office does not have the resources for

determining the actual cell density per square mm in the slides taught by Bubendorf and it is noted that cell density is dependent upon the amount of cells in the original sample and the amount of sample loaded for cytospinning, such that any slides prepared would have a variety of cell densities. Furthermore, it appears that such cytospinning methods were commonly practiced in the art and because there is an unknown random amount of cells in the original sample some slides prepared by the methods of Bubendorf would also randomly have a density of 300-500 cells per square mm, absent a showing otherwise. For these reasons, cytospinning the samples to a density of 300-500 cells per square mm is also considered to be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

9. Claim 84 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bubendorf et al (Am J Clin Pathol., 116:79-86, 2001, of record) in view of Brown (Urol. Clin. NA., 27(1):25-37, 2000, of record), as applied to Claims 72, 73, 82, 87, 89, 91 and 93 above, and further in view of US Patent 6,418,236 (Ellis et al, July 9, 2002, of record) or Kaplinsky (43rd ASH Annual Meeting, Blood, 98(Part 2):348b, 2001, IDS filed 4/9/08).

Claim 84 is further drawn herein to said imaging being effected using an automated cell imaging device capable of at least dual imaging.

Bubendorf et al in view of Brown teach and render obvious methods as set forth in the above rejection of claims under 35 U.S.C. 103(a).

These references do not expressly teach imaging cells with an automated imaging device capable of dual imaging.

This deficiency is made up for in the teachings of US Patent 6,418,236 or Kaplinsky. US Patent 6,418,236 teaches automated image analysis using a microscope capable of dual imaging to image cells stained with two stains, such as morphological stains and in situ hybridization stains which can be fluorescent stains (see entire document, e.g., column 1, lines 26-59, column 4, lines 31-67, column 5, lines 1-15).

Kaplinsky teaches automated image analysis using a microscope capable of dual imaging to image the same cells stained with a morphological stain and fluorescent in situ hybridization (FISH) stains (see entire document, e.g., abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to identify transitional cell carcinoma cells from a voided urine sample using the processes rendered obvious by Bubendorf et al in view of Brown and additionally imaging the stained cells with an automated microscope capable of dual imaging to identify the same single cells as transitional cell carcinoma cells.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to identify transitional cell carcinoma cells by such processes because the stains and processes of Bubendorf et al and Brown were known in the art to identify transitional cell carcinoma cells while the automated imaging microscope of US Patent 6,418,236 would allow for faster processing of samples. For example, US Patent 6,418,236 teaches that automated imaging analysis "eliminates the need for operator input to locate biological objects or areas of interest for analysis" (see column 8, lines 30-32). Additionally, Kaplinsky teaches that automated imaging analysis "provides two important features: scanning large number of cells, and performing combined analysis of morphology and FISH on the same cells" (see abstract, lines 6-8). Thus, there would be an advantage and a reasonable expectation of success in identifying transitional cell carcinoma cells from a voided urine sample, by additionally imaging the stained cells with an automated microscope capable of dual imaging as taught by US Patent 6,418,236 or Kaplinsky to identify the same single cells as transitional cell carcinoma cells, in view of the references.

For these reasons, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

10. No claim is allowed.

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Ishiwata et al (Urol., 57:811-815, 2001) discloses a method of identifying transitional cell carcinoma cells and diagnosing bladder cancer in cells stained with morphological stains and FISH stains. Haerlach et al (Blood, 6:2459-2463, 1996) teach methods of visualizing stains in the same single cells stained with Giemsa and FISH stains. Placer et al (of record) discloses a method of identifying transitional cell carcinoma cells and diagnosing bladder cancer in cells stained with standard Papanicolaou stain and FISH stains. Halling et al (of record) discloses a method of identifying transitional cell carcinoma cells and diagnosing bladder cancer in cells stained with FISH stains. Inoue et al (of record) teach methods of identifying transitional cell carcinoma cells or diagnosing bladder cancer in the same single cells obtained from a urine sample wherein the cells are stained with Giemsa and FISH chromosome 9 stains. Darzynkiewicz et al (of record) discloses an automated cell-imaging device capable of dual imaging. Shimoni et al (of record) discloses an automated cell-imaging device capable of dual imaging of cells stained with a May-Grunwald-Giemsa stain and FISH probes. Boon et al (of record) discloses a method of identifying transitional cell carcinoma cells and diagnosing bladder cancer in cells stained with a Giemsa stain or a Papanicolaou stain. Otto et al (of record) discloses a method of identifying transitional cell carcinoma cells and diagnosing bladder cancer in cells stained with a Hematoxylin stain and an Eosin stain. US Patents 6,174,681 (2001), 6,376,188 (2002) and 7,232,655 (2007) (all Halling et al) disclose a method of identifying transitional cell carcinoma cells and diagnosing bladder cancer in the same single cells stained with a morphological stain, such as DAPI and FISH stains. Placer et al (of record) discloses a method of identifying transitional cell carcinoma cells and diagnosing bladder cancer in cells stained with standard Papanicolaou stain or FISH stains. Dalquen et al (of record) discloses a method of identifying transitional cell carcinoma cells and diagnosing bladder cancer in cells stained with standard Papanicolaou stain or FISH stains.

Sokolova et al (of record) discloses a method of identifying transitional cell carcinoma cells and diagnosing bladder cancer in the same single cells stained with DAPI and FISH stains. Mezzelani et al (of record) discloses a method of identifying transitional cell carcinoma cells and diagnosing bladder cancer in the same single cells stained with DAPI and FISH stains.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Thursday, 6:15 AM to 4:45 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on (571) 272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

/bd/
Examiner, Art Unit 1643
June 28, 2011

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/Misook Yu/

Supervisory Patent Examiner, Art Unit 1642